CLINICAL MICROBIOLOGY REVIEWS, July 1990, p. 280–291
0893-8512/90/030280-12$02.00/0

Vol. 3, No. 3

Resistance to Vancomycin and Teicoplanin: an Emerging Clinical Problem

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INTRODUCTION

In the early 1950s, therapy of infections due to *Staphylococcus aureus* was threatened by the increasing prevalence of "hospital" strains of *S. aureus* resistant to penicillin (33, 51, 106) due to their production of penicillinase (5). Administration of tetracycline, erythromycin, or other therapeutic alternatives was also followed by emergence of strains of *S. aureus* resistant to these agents (30–32, 66). In many centers, 40 to 80% of hospitalized patients were found to be colonized with resistant *S. aureus*, including multiply resistant strains (61, 93, 121). Furthermore, a real increase in staphylococcal cross-infection appeared to accompany the use of penicillin and other antimicrobial agents and the emergence of penicillin-resistant *S. aureus* (8, 55). Strains that were multiply resistant tended to be more virulent or to spread more readily (121). Such reports were the stimulus for pharmaceutical companies to search for novel agents with specific antistaphylococcal activity. In 1956, at Eli Lilly & Co., a product from broth cultures of a previously unknown actinomycete, *Streptomyces orientalis*, isolated from a soil sample from Borneo, proved inhibitory at low concentrations for all strains of staphylococci examined (20, 69). The compound was also active against all other gram-positive organisms examined (28, 35, 45, 118). Further development of this product was assured when it was demonstrated that evolution of resistance to it in vitro in strains of *S. aureus* was rare and insignificant when it occurred (45, 128) and its animal toxicity was negligible (2). The compound was allocated the generic name vancomycin (derived from the word vanquish). In limited clinical trials, successful microbiological and clinical responses following the use of vancomycin led to its approval by the Food and Drug Administration in 1958 and to its widespread use in the succeeding 2 years.

Toxicity (3, 39, 70, 113) and adverse reactions during administration (50, 78) of early preparations of vancomycin led to a decrease in its use after the introduction during the 1960s of methicillin and other penicillinase-stable penicillins and cephalosporins. Over the succeeding 20 years, vancomycin was used mainly for the treatment of staphylococcal and streptococcal infections in patients allergic to penicillins. However, in recent years, the value of methicillin and other penicillinase-stable β-lactam antimicrobial agents has been compromised by the emergence and subsequent spread, particularly in hospitals, of methicillin-resistant staphylococci, both coagulase positive and coagulase negative (59, 109, 117). Vancomycin has thus again become widely used for the management of staphylococcal infections when such strains are prevalent. In addition, vancomycin is advocated for use prophylactically and therapeutically in a number of clinical settings when patients may be at risk from infection with multiresistant gram-positive species such as *S. epidermidis* or *Corynebacterium jeikeium*. These include patients having peritoneal dialysis (74, 81) or hemodialysis (26, 58) and those with prosthetic devices, catheters, or implants (124). In addition, oral vancomycin is of value in the treatment of pseudomembranous colitis (13, 29) and has been used as a component of bowel decontamination regimens (9).

The resurgence of interest in vancomycin has been accompanied by a research program in the pharmaceutical industry aimed at discovering and developing other glycopeptide antimicrobial drugs. Several glycopeptides are being evaluated (103) and one compound, teicoplanin, is undergoing phase 3 clinical investigation. Teicoplanin (formerly teicho-

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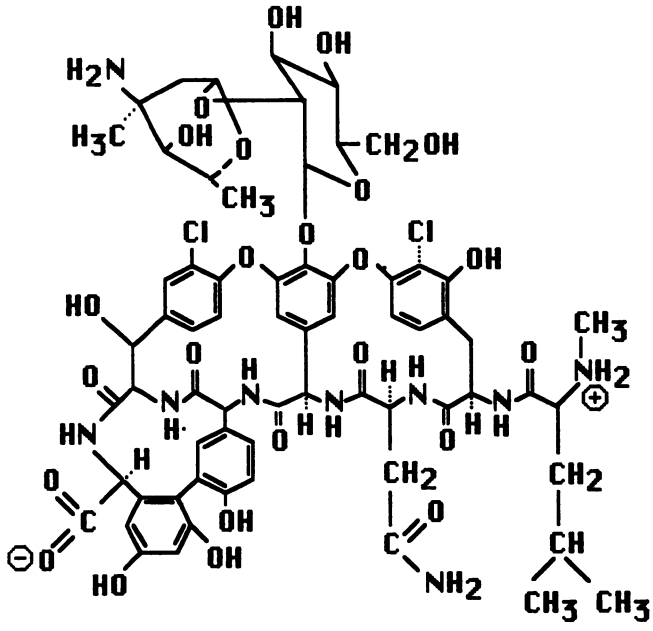

FIG. 1. Structure of vancomycin.

mycin A2) is a complex of glycopeptides obtained from fermentation broths of *Actinoplanes teichomyceticus* (*Streptomyces teichomyceticus*) (87) and, like vancomycin, is inhibitory for most gram-positive bacteria (43).

In 1986, Cooper and Given published a comprehensive review of 30 years of clinical experience with vancomycin, which highlighted the fact that there had been no trend towards vancomycin resistance (20). Although there had been a number of reports of strains of glycopeptide-resistant *S. aureus* (28, 44, 60, 89, 100), enterococci (49, 112), and coagulase-negative staphylococci (18, 114), the numbers of such strains were small and their clinical significance was not assessed. Since 1986, however, there have been indications that this situation is changing, as evidenced by reports of the isolation from clinical material of gram-positive bacteria resistant to vancomycin or teicoplanin or both. The purpose of this article is to review the emerging clinical problem of resistance to glycopeptide antimicrobial agents.

STRUCTURES AND MODES OF ACTION OF VANCOMYCIN AND TEICOPLANIN

Vancomycin (Fig. 1) is a tricyclic glycopeptide consisting of two chlorinated β-hydroxytyrosine moieties, asparagine, *N*-methyl-leucine, and three substituted phenyl-glycine moieties, one of which is substituted with a disaccharide composed of glucose and the unique amino sugar vancosamine (90). Teicoplanin (Fig. 2) is structurally related to vancomycin except that asparagine and *N*-methyl-leucine are replaced by linked hydroxyphenyl-glycine moieties, which give the molecule a tetracyclic rather than tricyclic structure and three sugars, mannose, *N*-acetylglucosamine, and *N*-acylglucosamine, are attached to the aryl groups (86). The acyl substituent of the *N*-acylglucosamine is a fatty acid and contains 10 or 11 carbon atoms (Fig. 2). Teicoplanin is a mixture of five structurally related molecules (designated TA2-1 to TA2-5) together with a more polar product designated TA-3 (10). The components of the TA2 complex, which constitute 90 to 95% of teicoplanin, differ only in the structure of the fatty acid acyl component of the *N*-acylglucosamine (Fig. 2).

As might be expected on the basis of their chemical similarity, vancomycin and teicoplanin possess a similar mechanism of antimicrobial activity, selectively directed against gram-positive bacteria (43, 85, 118). Both compounds inhibit peptidoglycan synthesis (86, 92) by interacting with the terminal D-alanyl-D-alanine present on the pentapeptide side chains of the peptidoglycan precursors (82, 108). This interaction appears to involve formation of hydrogen bonds between the two molecules, with part of the glycopeptide molecule forming a cleft or pocket which encloses the D-alanyl-D-alanine region (92). It is postulated that the presence of the relatively large molecules of vancomycin (molecular weight, 1,448) or teicoplanin (molecular weight, approximately 1,900) enclosing the D-alanyl-D-alanine region of the pentapeptide side chain sterically inhibits further enzyme-mediated peptidoglycan polymerization (92).

The relatively large size of glycopeptides is thought to contribue to their selective activity against gram-positive bacteria. Although gram-negative bacteria contain peptidoglycan in their cell walls, the D-alanyl-D-alanine target sites are protected by the outer membrane, which is impermeable to these large predominantly polar antimicrobial molecules. Hydrophilic molecules may cross the outer membrane through porins, but the exclusion size of these channels is about 600 daltons, which is well below the size of vancomycin and teicoplanin (92).

In addition to its effect on peptidoglycan synthesis, vancomycin has been shown to alter the permeability of the cytoplasmic membrane (46) and may inhibit RNA synthesis (56), although the mechanisms involved have not been fully elucidated.

BACTERIA RESISTANT TO VANCOMYCIN AND OTHER GLYCOPEPTIDE ANTIMICROBIAL AGENTS

Resistance to vancomycin or teicoplanin or both has been detected in six genera of gram-positive bacteria: *Leuconostoc*, *Lactobacillus*, *Pediococcus*, *Erysipelothrix*, *Enterococcus*, and *Staphylococcus*.

Leuconostoc

Leuconostocs are gram-positive, nonmotile, nonsporeforming, facultatively anaerobic cocci commonly found in dairy products and on plants (36). Until recently, *Leuconostoc* spp. were not considered to be pathogenic for humans (36), but during the last few years there have been a number of individual reports of their isolation from clinical sources (Table 1). A common feature of these reports has been that the organisms have exhibited high-level resistance (MIC, >128 mg/liter) to vancomycin. A group of 50 strains resistant to vancomycin (showing no zone of inhibition around a 30-μg disk) and isolated from humans has also been reported (27). The further observation that *Leuconostoc* spp. from dairy and other nonclinical sources (including *Leuconostoc oenos*, *L. mesenteroides*, *L. cremoris*, and *L. dextranicum*) also exhibited resistance to vancomycin (83) indicates that such resistance may be an inherent property of this genus.

With the exception of a case of meningitis (21), patients from whom *Leuconostoc* spp. have been isolated were suffering from some underlying disease which may have predisposed them to opportunistic infection with organisms of low virulence. In most instances, the source of the infecting leuconostocs was unknown. Two babies who developed bacteremia with vancomycin-resistant leuconostocs had intravascular catheters which were colonized, but swabs

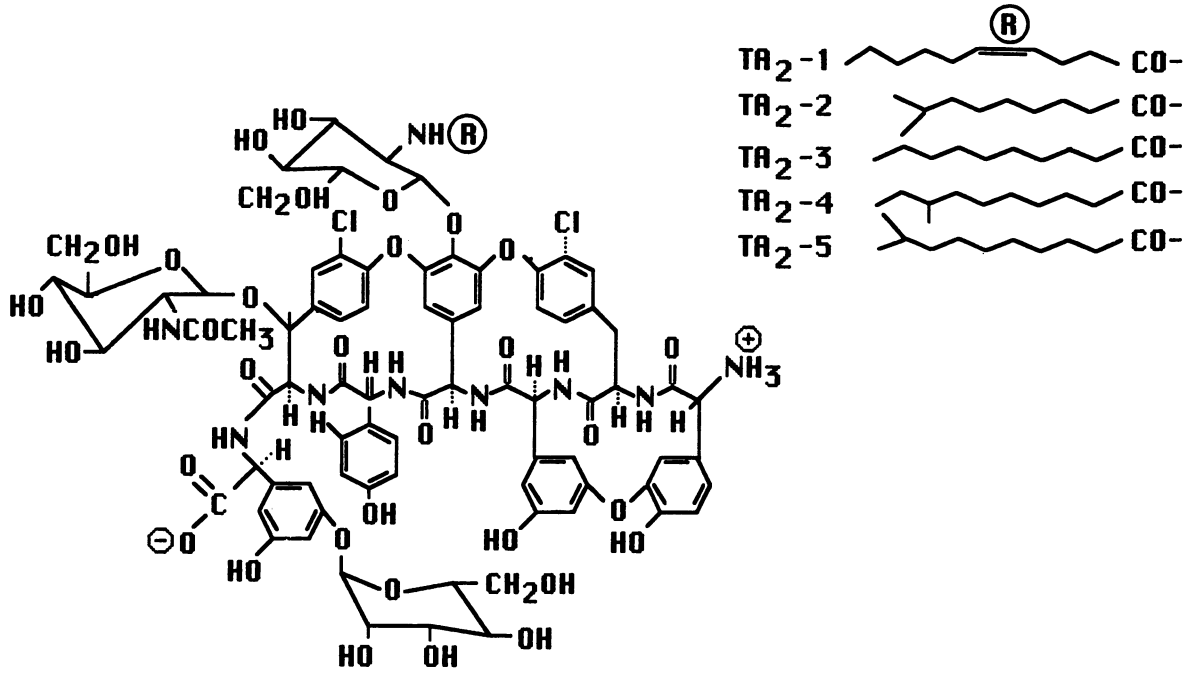

FIG. 2. Structure of teicoplanin.

obtained from the stool of one baby, the throats of staff, and environmental surfaces failed to yield similar organisms (48, 94). In another study involving three patients infected with vancomycin-resistant leuconostocs, swabs from the gingivae and skin of 22 hospital workers who were in contact with the patients failed to yield leuconostocs (54). Clearly, further studies are required if we are to understand the epidemiology of opportunistic infections caused by such organisms.

The results of antimicrobial susceptibility testing show that vancomycin-resistant *Leuconostoc* spp. are also resistant to teicoplanin (14, 21, 67, 79) but usually susceptible to a wide range of other compounds including various β-lactams, macrolides, and aminoglycosides (14, 21, 22).

Another feature noted in some of the reported cases of infection with strains of vancomycin-resistant *Leuconostoc* spp. was an initial misidentification of the organisms. For example, the leuconostoc isolate described by Coovadia et al. was first identified as *Streptococcus pneumoniae* (21). Other organisms with which leuconostocs have been confused include *Streptococcus sanguis* II (14, 54) and viridans streptococci (48). In all of these reports, the isolates were subsequently observed to produce gas in De Man, Rogosa, and Sharpe broth containing glucose, which precluded their identification as members of the genus *Streptococcus* (23). Their assignment to the genus *Leuconostoc* followed the results of carbohydrate fermentation tests, as well as hydrolysis and reduction of appropriate substrates (12, 36).

Lactobacillus

Lactobacilli are gram-positive, nonmotile, nonspore-forming, facultatively anaerobic bacilli which ferment sugars, forming lactate as an end product. They are found in dairy products, vegetables, and fruit and also comprise part of the normal flora of the mouth and intestinal and genital tracts of many animal species and humans (57). Recently,

TABLE 1. Isolation of glycopeptide-resistant *Leuconostoc* spp. from clinical material

Organism	Patient		Site of isolation	Vancomycin MIC (mg/liter)	Teicoplanin MIC (mg/liter)	Country[a]	Reference
	Age (yr)	Sex					
Leuconostoc spp.	16	F	Cerebrospinal fluid	>256	R[b]	South Africa	21
L. dextranum	36	F	Blood	>256	>256	France	14
Leuconostoc spp.	40	M	Blood	>256	>256	France	14
L. paramesenteroides	53	F	Blood	>256		USA	54
L. mesenteroides	78	F	Blood	>256		USA	54
L. paramesenteroides	3.5 mo	M	Blood	>256		USA	54
L. mesenteroides	1 mo	M	Blood	>128		USA	94
Leuconostoc spp.	56	F	Gastronomy site	>256		USA	96
Leuconostoc spp.	75	M	Gastronomy site	>256		USA	96
Leuconostoc spp.	83	M	Tracheostomy site	>256		USA	96
Leuconostoc spp.			Blood	>128	>128	FRG	67
Leuconostoc spp.			Wound	>128	>128	FRG	67

[a] USA, United States of America; FRG, Federal Republic of Germany.
[b] R, Resistant by disk test.

Ruoff and colleagues reported that 25 strains of lactobacilli isolated from clinical material, including stool samples, were all resistant to vancomycin (MIC, >256 mg/liter) (96). Some of the strains were isolated from patients' wounds or wound drains, but the lack of association with fever, leukocytosis, or cellulitis at the site of isolation suggested that they were not clinically significant. In three patients, however, vancomycin-resistant lactobacilli were recovered in mixed culture from body sites that are usually sterile (liver, abdominal cavity, and blood), indicating possible clinical significance. Holliman and Bone recovered vancomycin-resistant (MIC, >1,000 mg/liter) *Lactobacillus casei* subsp. *rhamnosus* from pus from a patient with an aortic graft which had ruptured and from blood from another patient with suspected endocarditis (52). Vancomycin-resistant lactobacilli isolated from blood cultures have also been described by other workers (G. Colman and A. Efstratiou, editorial, J. Hosp. Infect. **10**:1–3, 1987), although further detailed clinical information was not provided. The resistance of lactobacilli to vancomycin may be an inherent property of many strains belonging to this genus; three of four strains obtained from the American Type Culture Collection were resistant (MIC, >256 mg/liter) (*L. casei* subsp. *rhamnosus*, *L. fermentum*, and *L. plantarum* were resistant; *L. leichmannii* was susceptible) (96). Furthermore, each of 16 strains of *L. reuteri* and four of 20 strains of *L. acidophilus* isolated from pig or calf feces were reported to show vancomycin resistance, although the criteria used to define resistance were not provided (116). Facklam and co-workers found 38 of 42 human isolates of *Lactobacillus* spp. also to be resistant to vancomycin (no zone around a 30-μg disk) (27).

It is of interest that one plasmid-bearing, multiresistant strain of *L. acidophilus* lost its resistance to vancomycin, together with resistance to a number of other compounds, following elimination of plasmids by treatment with ethidium bromide or acriflavine (116). Thus, there is a possibility that, in this strain, at least, resistance to vancomycin was plasmid mediated.

A number of reports have documented resistance to vancomycin among organisms identified as streptococci, including viridans streptococci isolated from patients with endocarditis (4, 11) and a strain of *Streptococcus sanguis* II from a bacteremic patient (105). However, Thornsberry and Facklam (C. Thornsberry and R. R. Facklam, Antimicrob. Newsl. **1**:63–64, 1984) subsequently reported that a number of viridans streptococci which had been referred to their laboratory as showing resistance to vancomycin were all lactobacilli. They expressed the view that, in their experience, there was no evidence for vancomycin resistance among bona fide viridans streptococci. These workers and others (96) stressed the importance of assessing the morphology of broth-grown bacteria and noted that lactobacilli may appear coccoid in Gram-stained films prepared from organisms cultured on agar, with consequent problems of identification. A similar problem involving differentiation between streptococci and *Leuconostoc* spp. has been described above.

Pediococcus

Pediococci are lactic acid bacteria which divide alternately in two planes at right angles to form tetrads (37). Like other lactic acid bacteria, they are gram-positive, nonmotile, facultative anaerobes which do not form spores. Pediococci occur in dairy products, vegetable material, and alcoholic beverages and have been described as nonpathogenic for animals, including humans (37). Recently, however, three vancomycin-resistant strains isolated from human feces were described by Ruoff and colleagues (96), while three further vancomycin-resistant strains of human origin, submitted to the Streptococcus Reference Laboratory, Central Public Health Laboratory, Colindale, London, England, were reported by Colman and Efstratiou (Colman and Efstratiou, editorial, J. Hosp. Infect. **10**:1–3, 1987). In addition, Facklam and colleagues have reported that 26 strains of pediococci from human sources were each resistant to vancomycin (no zone around a 30-μg disk) (27). However, the clinical significance of pediococci is unclear at present.

Erysipelothrix

The genus *Erysipelothrix* contains only the type species, *Erysipelothrix rhusiopathiae* (91), a gram-positive, pleomorphic bacillus. It is nonmotile, nonsporing, facultatively anaerobic, and catalase negative. Its colonies may produce alpha-hemolysis on blood agar. It must be distinguished from viridans streptococci, lactobacilli, *Listeria monocytogenes*, and corynebacteria. In blood cultures, it has been misidentified as a viridans streptococcus and dismissed as a contaminating gram-positive rod. It is parasitic on a wide variety of mammals, birds, fish, and invertebrates. Some strains are pathogenic for mammals, including humans, and birds. Infections in humans are rare and are usually related to occupational exposure (40, 91), and present as localized (erysipeloid) or generalized cutaneous infections and/or a septicemic illness often associated with endocarditis. In a recent review, Gorby and Peacock reported that five strains were tested for vancomycin susceptibility (40). All five were resistant. MICs and MBCs for two of these strains were 25 and 50 mg/liter, respectively. Further strains need to be tested to determine whether vancomycin resistance is an inherent characteristic of the genus. This is important clinically since vancomycin, in combination with an aminoglycoside, is used as empiric therapy for the management of endocarditis due to gram-positive bacteria, particularly in patients allergic to penicillins.

Enterococcus

Enterococci constitute a normal component of the human gut flora but may invade and provoke opportunistic infections in compromised patients. Serious enterococcal infections, including bacteremia or endocarditis, may be difficult to treat, the recommended regimen being a penicillin plus an aminoglycoside (62). In patients in whom β-lactams cannot be used, either because of infection with β-lactam-resistant strains of enterococci or because of allergy to penicillins, vancomycin, often in combination with an aminoglycoside, may be the drug of choice (49, 62, 119, 120). It is, therefore, disturbing that since 1986 there have been a number of reports of the isolation of vancomycin-resistant enterococci from various parts of the world, including England, France, the United States, the Federal Republic of Germany, and Spain (Table 2).

Strains of four species of enterococci, namely, *Enterococcus faecalis*, *E. faecium*, *E. avium*, and *E. gallinarum*, have to date been reported to have resistance to vancomycin (Table 2). In the largest cluster of infections or colonizations described (115), three species were involved (*E. faecalis*, *E. faecium*, and *E. avium*). The infections or colonizations were nosocomial and confined to renal unit patients of a general hospital. Forty-one patients were immunocompro-

TABLE 2. Isolation of glycopeptide-resistant enterococci from clinical material

Organism	No. of strains	Vancomycin MIC (mg/liter)	Teicoplanin MIC (mg/liter)	Site of isolation	Country[a]	Yr of isolation	Reference(s)
E. faecalis	15	≥512	>64	Various[b]	UK	1986–87	115
E. faecalis	3	128	8–64	Various[b]	Spain	1987–88	Alonso et al.[c]
E. faecalis	1	≥128		Wound	Spain	1988	Reguera et al.[d]
E. faecalis	3	32–64	≤0.5	Blood, urine	USA	1987	97
E. faecalis	1	256	16	Urine	France	1988	104
E. faecalis	1	1,024		Blood	France	1988	7
E. faecium	27	≥512	>64	Various[b]	UK	1986–87	115
E. faecium	4	≥512	≥64	Feces	France	1986–88	63, 64
E. faecium	1	1,000	≥64	Blood	France	1988	102
E. faecium	1	32	0.5	Urine	France	1987	122
E. faecium	1	32	0.5	Peritoneum	FRG	1987	67
E. faecium	1	≥128		Wound	Spain	1988	Reguera et al.[d]
E. faecium	1	>256	32	Not known	Spain	1987	47
E. avium	3	≥64	≥64	Various[b]	UK	1987	115
E. gallinarum	1	16	1	Blood, wound	USA	1987	58

[a] UK, United Kingdom; USA, United States of America; FRG, Federal Republic of Germany.
[b] Includes isolation from blood.
[c] Alonso et al., Abstr. 4th Eur. Congr. Clin. Microbiol. 1989, abstr. no. 411, p. 175.
[d] Reguera et al., Abstr. 4th Eur. Congr. Clin. Microbiol. 1989, abstr. no. 614, p. 275.

mised due to the uremia of end-stage renal failure and, in some, their immunosuppressive drug regimens. Some 56% of the group had had vancomycin therapy recently or at the time of isolation of their vancomycin-resistant enterococci. More than 90% had received or were receiving a cephalosporin which may have rendered them susceptible to colonization or superinfection with enterococci. Cases were clustered geographically and temporally, suggesting that cross-infection might have occurred. In the case reported by Kaplan and colleagues, the patient from whom vancomycin-resistant *E. gallinarum* was isolated was undergoing hemodialysis and had received prophylaxis with vancomycin (58). When clinical details are available for other patients from whom vancomycin-resistant enterococci have been isolated, there are many features common to the renal unit cluster: these include lengthy inpatient stay, immunosuppression, exposure to cephalosporins, and usage within the patient subset of vancomycin but not necessarily as therapy for the affected individual (63, 64, 97).

Analysis of the MICs of vancomycin and teicoplanin for the vancomycin-resistant enterococci reported to date indicates that resistance in these organisms falls into two categories. One category, which includes strains of *E. faecalis*, *E. faecium*, and *E. avium*, is characterized by high-level resistance to both vancomycin (MIC, 64 to >2,000 mg/liter) and teicoplanin (MIC, ≥8 mg/liter) (7, 47, 63, 64, 102, 104, 115; J. A. Reguera, J. C. Perez-Diaz, M. Martinez-Ferer, and F. Baquero, Abstr. 4th Eur. Congr. Clin. Microbiol. 1989, abstr. no. 614, p. 275; T. Alonso, J. Linares, R. Martin, P. Lopez, D. Garcia, and E. Escribano, Abstr. 4th Eur. Congr. Clin. Microbiol. 1989, abstr. no. 411, p. 175), while the other category is characterized by lower-level resistance to vancomycin (MIC, 32 to 64 mg/liter) and susceptibility to teicoplanin (MIC, ≤1 mg/liter). The latter group includes strains of *E. faecalis* (97), *E. faecium* (67, 103, 122, 125), and *E. gallinarum* (58). As described in more detail below, there is now evidence that these two categories of vancomycin-resistant enterococci differ with regard to both genotypic and phenotypic bases of glycopeptide resistance.

Staphylococcus

S. aureus is an important cause of both nosocomial and community-acquired infection. The increasing occurrence, particularly in hospitals, of *S. aureus* resistant not only to methicillin but to a wide range of antimicrobial agents, including newer agents such as ciprofloxacin (68), has meant that therapy has become more difficult. Against this background, vancomycin and teicoplanin, with their antistaphylococcal activity, have been used to an increasing extent. The lack of resistance to vancomycin and teicoplanin among strains of *S. aureus* is exemplified by two recent surveys which failed to detect resistance among 106 strains of multiresistant, methicillin-resistant *S. aureus* from 21 countries (68) and 169 multiresistant strains from the state of New York (41).

In addition to *S. aureus*, coagulase-negative staphylococci are now recognized to be an important cause of infection including nosocomial bacteremia and infection of foreign bodies such as indwelling catheters and prosthetic heart valves (59, 71, 114). Coagulase-negative staphylococci are also a common cause of peritonitis in patients undergoing continuous ambulatory peritoneal dialysis (84, 126). As with *S. aureus*, resistance to methicillin and other antimicrobial agents has been seen increasingly among coagulase-negative staphylococci and has meant that vancomycin has become a drug of choice in the treatment of infections due to them. In contrast to the situation seen with *S. aureus*, however, there have been a number of reports of the isolation of glycopeptide-resistant, coagulase-negative staphylococci. In 1981, Cherubin and colleagues reported that MICs of vancomycin for 30 clinical strains of *S. epidermidis* ranged from 2 to >16 mg/liter (18). Two years later, Tuazon and Miller described eight patients with septicemia, endocarditis, or osteomyelitis from whom strains of *S. epidermidis* with MICs of vancomycin of 10 to 20 mg/liter were isolated (114). The susceptibility of these strains to teicoplanin was, however, not assessed. More recently, a case was reported of the failure of vancomycin alone to cure a patient with peritonitis caused by *S. haemolyticus* (101). Eight isolates of *S. haemolyticus* obtained from the patient over an 88-day period showed a

gradual increase in resistance to vancomycin from an initial MIC of 2 mg/liter to one of 8 mg/liter (101). It is of interest that the first isolate from this patient was resistant to teicoplanin (MIC, 16 mg/liter), but susceptible to vancomycin (MIC, 2 mg/liter). The seven subsequent isolates, showing an increase in vancomycin MIC from 2 to 8 mg/liter, showed no significant change in the MIC of teicoplanin. This raises the possibility that coagulase-negative staphylococci of reduced susceptibility to teicoplanin may develop vancomycin resistance more readily than strains fully susceptible to teicoplanin.

There have been other reports of the isolation of coagulase-negative staphylococci exhibiting resistance to teicoplanin but susceptibility to vancomycin (42, 123). Wilson and colleagues isolated a teicoplanin-resistant (MIC, 16 mg/liter) strain of *S. epidermidis* from a pacing-wire tip removed 8 days after repair of a ventricular septal defect under teicoplanin prophylaxis. The MIC of vancomycin for the strain was 2 mg/liter. Although the organism was present on the pacing-wire tip, the patient did not have an associated infection (123). Subsequently, Grant and co-workers reported the isolation of 12 strains of commensal coagulase-negative staphylococci with MICs of teicoplanin of 12.8 to 25 mg/liter (42). The MICs of vancomycin were 0.8 to 1.6 mg/liter. In addition, they described a teicoplanin-resistant (MIC, 12.8 mg/liter), vancomycin-susceptible (MIC 1.6 mg/liter) strain of *S. epidermidis* recovered from a patient with peritonitis (42). Two further teicoplanin-resistant (MIC, 10 mg/liter) strains of coagulase-negative staphylococci have also been reported, although the susceptibility of these isolates to vancomycin was not assessed (15). The strains were isolated from patients during a trial of teicoplanin in the treatment of severe staphylococcal sepsis.

STUDIES OF THE MOLECULAR BASIS OF RESISTANCE TO VANCOMYCIN AND TEICOPLANIN

Genetic Studies

To assess the potential risk of dissemination of resistance to glycopeptides among susceptible bacterial populations, several groups of investigators have examined the ability of vancomycin-resistant enterococci to transfer resistance in vitro. Leclercq and colleagues initially showed that the genes for resistance in each of two clinical isolates of vancomycin-resistant *E. faecium* were located on plasmids (63). Although the plasmids were not transferable by conjugation to *E. faecalis* JH2-2 or BM4110, the plasmid from one strain could be transferred to a recipient strain of *E. faecium*. In addition, purified plasmid DNA from both strains transformed *Streptococcus sanguis* Challis to vancomycin and teicoplanin resistance. In a subsequent report, the same research group reported the isolation of two further strains of vancomycin-resistant *E. faecium* in which resistance to vancomycin and teicoplanin could also be transferred to a recipient strain of *E. faecium* (BM4107) by conjugation (64). Analysis of transconjugants by agarose gel electrophoresis revealed the presence of transferred plasmids. A further series of mating experiments showed that one of the two strains could also transfer the plasmid-encoded glycopeptide resistance to a range of other gram-positive bacteria, including *Streptococcus sanguis*, *Streptococcus lactis*, *Streptococcus pyogenes*, and *Listeria monocytogenes*. However, attempts to transfer vancomycin resistance to *S. aureus* or *Bacillus subtilis* have been unsuccessful (64). Plasmid-mediated transferable vancomycin resistance in *E. faecium* has also been reported from workers in Spain (Reguera et al., Abstr. 4th Eur. Congr. Clin. Microbiol. 1989, abstr. no. 614, p. 275).

Three other groups have also demonstrated transferable resistance to glycopeptides in *E. faecium*. Shlaes and colleagues reported that *E. faecium* D399 transferred resistance to vancomycin and teicoplanin to *E. faecalis* JH2-2 (102). In contrast to the studies described above, however, plasmids were not detected in either the donor strain or transconjugants, suggesting that the resistance gene may have been encoded on the chromosome, possibly in association with a transposon. Transferable glycopeptide resistance was also reported in two strains of *E. faecium* by Uttley and coworkers (115). In this study, the two donor strains, which harbored three and four plasmids, respectively, each transferred a single plasmid of 24 megadaltons to the recipient strain of *E. faecalis*, JH2-2. The transconjugants also acquired resistance to erythromycin and chloramphenicol, suggesting that this plasmid encoded resistance to these antimicrobial agents as well as resistance to vancomycin and teicoplanin. However, a cured variant of one of these *E. faecium* strains, which simultaneously lost resistance to all of these antimicrobial agents, retained the full plasmid content of the parent strain (115). Thus, the location of the glycopeptide resistance determinant in these strains is unclear. Recently, Handwerger and colleagues showed that a plasmid encoding high-level glycopeptide resistance in a strain of *E. faecium* also conferred a response to pheromones produced by recipient strains of *E. faecalis* and *Streptococcus sanguis*, although resistance was transferred only to the former (47). This is the first report of a pheromone response plasmid in *E. faecium* (47).

Uttley and colleagues also reported interstrain transfer of glycopeptide resistance in *E. faecalis* in vitro (115). Although the donor strain contained a 40-megadalton plasmid, plasmids were not detected in the glycopeptide-resistant transconjugants which also acquired resistance to erythromycin. Shlaes and colleagues also reported transferable vancomycin resistance in *E. faecalis* 256 (104). Although the donor strain contained four plasmids, 17 of 20 transconjugants tested were plasmid-free. It is possible, therefore, that resistance to vancomycin and teicoplanin in this strain of *E. faecalis* was encoded on the chromosome, although the involvement of conjugative transposons needs to be considered (19, 34). In contrast to these findings, Reguera and colleagues described a strain of *E. faecalis* in which transferable vancomycin resistance was associated with transfer of a 40-kilobase plasmid (Reguera et al., Abstr. 4th Eur. Congr. Clin. Microbiol. 1989, abstr. no. 614, p. 275).

Recently, the gene coding for high-level resistance to vancomycin and teicoplanin in a strain of *E. faecium* has been cloned (S. Dutka-Malen, A. Brisson-Noel, C. Molinas, and P. Courvalin, Progr. Abstr. Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 272, 1989). The cloned gene, designated *vanA*, has been sequenced, and a 290-base-pair probe specific for *vanA* has been prepared. When this probe was used in a dot blot hybridization assay, the *vanA* gene was found to be present in strains of *E. faecium* and *E. faecalis* showing high-level resistance to vancomycin and teicoplanin. In contrast, the probe failed to hybridize with strains of *E. faecalis* and *E. gallinarum* showing lower-level vancomycin resistance and teicoplanin susceptibility. The probe also failed to hybridize with leuconostocs, lactobacilli, and pediococci, which appear to be inherently resistant to glycopeptides, or to teicoplanin-resistant coagulase-negative staphylococci (R. Leclercq, V. Coutant, S. Dutka-Malen, J.

Duval, and P. Courvalin, Progr. Abstr. Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 273, 1989).

Biochemical Studies

Attempts have been made to detect production of glycopeptide-inactivating enzymes by vancomycin-resistant organisms. By using microbiological assays based on the concept that inactivated vancomycin would fail to inhibit growth of a susceptible bacterial strain, production of vancomycin-inactivating enzymes could not be detected in strains of *E. faecalis* (104, 115), *E. faecium* (63, 64, 102, 115), or *Leuconostoc* spp. (83).

Some initial insight into the mechanism of glycopeptide resistance among enterococci was provided by the observation that the resistance is inducible (64, 80, 102, 122). When actively growing cells were diluted in medium containing subinhibitory concentrations of vancomycin, a lag phase of several hours occurred before cell division and growth of the culture resumed. In contrast, organisms preexposed to vancomycin and similarly diluted in vancomycin-containing medium showed no lag phase.

Biochemical anslysis, using sodium dodecyl sulfate-polyacrylamide gel electrophoresis, revealed that induction of resistance to vancomycin or other glycopeptides correlated with the synthesis of novel proteins in the cytoplasmic membrane. In initial studies with both *E. faecium* and *E. faecalis* exhibiting high-level resistance to vancomycin and teicoplanin, the novel protein was shown to have a molecular weight of 39,000 (80, 102, 104). Subequently, Williamson et al. repoted that the novel protein induced in *E. faecium* D366 (a strain showing lower-level resistance to vancomycin and susceptibility to teicoplanin) reproducibly differed in size, having a molecular weight of 39,500 (122). Further analysis involving comparison of the peptide profiles produced by partial proteolysis, as well as assessment of antigenic cross-reactivity by immunoblotting, revealed that the 39,000 and 39,500-dalton proteins were not structurally or antigenically related (S. Al-Obeid, L. Gutman, D. Shlaes, and E. Collatz, Progr. Abstr. Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 274, 1989). Despite this, recent studies indicate that both novel proteins bind to, and enzymatically modify, the pentapeptide side chains of peptidoglycan, preventing glycopeptides from interacting with their targets (1).

It is of interest that strains of both *E. faecalis* and *E. faecium* grown in media containing vancomycin exhibited inducible resistance not only to vancomycin, but also to teicoplanin and the other novel glycopeptides 62208, 62211, and 62476 (104, 122). Variable results were obtained, however, when the ability of the other glycopeptides to induce either self-resistance or resistance to vancomycin was assessed. Shlaes and colleagues who worked with *E. faecalis* A256 (104) found that all glycopeptides tested except teicoplanin induced varying degrees of self-resistance, while Williamson et al., who used *E. faecium* D366 (122), reported that glycopeptide 62208 induced resistance both to itself and to vancomycin, but that similar activity was not seen with glycopeptide 62211 or teicoplanin. In contrast, Nicas et al. reported that teicoplanin was an effective inducer of resistance to vancomycin in both *E. faecium* and *E. faecalis* (79). Clearly, further work is needed to determine whether the discrepancies between these studies reflect differences in experimental methods or interstrain variation in the susceptibility of enterococci to induction of glycopeptide resistance.

In contrast to enterococci, organisms such as leuconostocs, lactobacilli, or pediococci, which are apparently inherently resistant to vancomycin, do not require induction for resistance to be expressed (79). The addition of vancomycin to growing cultures of such organisms is not accompanied by a lag phase in their growth rate. Furthermore, antiserum prepared against the inducible 39,000-dalton protein present in a strain of glycopeptide-resistant *E. faecium* failed to react with membranes prepared from *Leuconostoc mesenteroides*, *L. citreum*, *L. lactis*, *L. confusus*, *Pediococcus acidi-lacti*, or *P. pentosaceus*, all of which exhibited constitutive high-level resistance to both vancomycin (MIC, >1,000 mg/liter) and teicoplanin (MIC, ≥256 mg/liter) (79). These findings, together with the observation that the cloned *vanA* gene failed to hybridize with inherently resistant species (Dutka-Malen et al., 29th ICAAC), suggest that the mechanism(s) involved in glycopeptide resistance in these organisms is distinct from that operating in enterococci showing high-level resistance.

FUTURE CONSIDERATIONS

Problems in Monitoring the Prevalence of Glycopeptide-Resistant Bacteria

With the excepton of inherently resistant genera and a few staphylocci, clinically significant glycopeptide resistance is at present confined to enterococci. Although such resistance has been reported from Europe, including England, and the United States, the number of strains in individual reports has been small. The exception is the collection of strains causing infection in a renal unit in southeast London (115). Two points, however, must be borne in mind. First, it is unclear as to whether or not resistance to vancomycin and teicoplanin has been underreported. As recently as early 1986, it was held that, since resistance had not been documented among normally susceptible bacterial species, it was rarely necessary to perform susceptibility tests with vancomycin or teicoplanin on clinical isolates (6). Second, the observations described above, that resistance to glycopeptides is transferable between strains in vitro, give cause for concern, as they suggest that glycopeptide resistance may be transferred similarly in nature, with a resulting increase in prevalence. Therefore, there is a need for an active program of surveillance by hospital and reference laboratories if resistance to vancomycin is to be monitored accurately.

Screening for high-level vancomycin and teicoplanin resistance among enterococci presents no real difficulties as such strains show no zone round a 30-μg disk. However, difficulties may arise with strains showing lower-level glycopeptide resistance as the interpretative criteria for disk testing have varied during the course of the last few years. In 1986, Barry et al. (6) recommended that, for tests with 30-μg vancomycin disks, zone diameters of ≤10 mm indicated resistance (MIC, >8.0 mg/liter) and zone diameters of ≥15 mm indicated susceptibility (MIC, ≤4.0 mg/liter). (With 30-μg teicoplanin disks, they recommended breakpoint zone sizes for resistance [MIC, >8 mg/liter] and susceptibility [MIC, ≤4 mg/liter] of ≤10 and ≥14 mm, respectively.) These represented a minor modification of the previously recommended standards for vancomycin of ≤9 and ≥12 mm (76). Subsequently, however, some enterococci for which MICs of vancomycin were 8 to 16 mg/liter were encountered which appeared to be susceptible by disk testing, producing zones of 17 to 18 mm (111). In view of these findings, as well as reports of emerging resistance to glycopeptides, Swenson

TABLE 3. Susceptibility of vancomycin-resistant enterococci isolated at Dulwich Hospital to various antimicrobial agents

Species	No. of strains	No. of strains resistant to indicated antimicrobial agent (breakpoint MIC, mg/liter)[a]									
		Amp (>8)	Chl (>8)	Cip (>4)	Cli (>1)	Ery (>1)	Fus (>4)	Rif (>2)	Tet (>2)	Tmp (>2)	Gen (HL) (>1,000)
E. faecalis	15	0	13	1	15	15	12	3	15	15	13
E. faecium	27	27	25	6	27	26	21	23	25	25	0
E. avium	3	2	0	0	1	1	3	1	2	1	0
Total (%)	45 (100)	29 (64)	38 (84)	7 (16)	43 (96)	42 (93)	36 (80)	27 (60)	42 (93)	41 (91)	13 (29)

[a] Amp, Ampicillin; Chl, chloramphenicol; Cip, ciprofloxacin; Cli, clindamycin; Ery, erythromycin; Fus, fusidic acid; Rif, rifampin; Tet, tetracycline; Tmp, trimethoprim; Gen (HL), high-level gentamicin.

and colleagues reevaluated the use of the disk diffusion test for detection of vancomycin resistance among enterococci (111). These workers found that application of the 1987 National Committee for Clinical Laboratory Standards criteria (77) resulted in strains for which MICs were 8 to 32 mg/liter being incorrectly classified as either susceptible or of intermediate resistance. Analysis of the results obtained with 53 strains of enterococci showed both major errors (e.g., a strain for which the MIC was 32 mg/liter was classified as susceptible by disk diffusion) and minor errors in 1.9 and 11.5% of the strains, respectively. When the same data were analyzed by using the criteria recommended by Barry et al. (6), 13.5% minor but no major errors were observed. Swenson and colleagues (111) suggested that using disk diffusion breakpoints of ≥15 mm for susceptibility and ≤14 mm for resistance would eliminate the problem of incorrectly classifying as susceptible strains for which MICs are 32 mg/liter, but would not affect the problems associated with the classification of strains for which MICs are 8 mg/liter. For these strains, they recommended that MIC determinations be carried out to differentiate them from susceptible strains for which MICs are ≤4 mg/liter (111). It is not clear at present how these recommendations, based primarily on work with enterococci, would affect assessment of susceptibility of other gram-positive species, such as the strain of *S. haemolyticus* with low-level resistance reported by Schwalbe et al. (101). It may be prudent to consider, at least with enterococci, spot inoculation onto susceptibility testing media containing 4 mg of vancomycin per liter as an adjunct to disk testing. Ideally, strains showing growth on such screening plates should then be examined by MIC techniques. In addition, the identity of such strains should be confirmed fully, to differentiate reliably enterococci and other streptococci from inherently resistant organisms such as pediococci, lactobacilli, and leuconostocs (27).

An automated system (AMS Vitek) for the rapid determination of antimicrobial susceptibilities failed to detect low-level vancomycin resistance in three strains of *E. faecalis* (97). This might reflect the short incubation period of this test which may not have provided sufficient time for the induction and expression of resistance (104). This problem is likely to apply equally to the detection of low-level resistance in *E. faecium* and of high-level resistance in all enterococci when short incubation times are used.

In a study by Felmingham and colleagues, MICs of vancomycin for *S. epidermidis* and *S. haemolyticus* were found not to be affected significantly by differing susceptibility test media, the presence or absence of blood, or the size of the inoculum used (D. Felmingham, K. Solomanides, M. D. O'Hare, A. P. R. Wilson, and R. N. Gruneberg, letter, J. Antimicrob. Chemother. **20**:609–610, 1987). In contrast, these variables resulted in large differences in the MICs of teicoplanin observed for the same species. A standardized approach for estimation of teicoplanin MICs is therefore required.

Management of Patients Colonized or Infected with Bacteria Resistant to Glycopeptides

The response of clinicians and microbiologists to the isolation of glycopeptide-resistant bacteria from patients and their subsequent management will depend on a number of factors. Such factors include the clinical setting; the particular species isolated, whether in pure or mixed culture; and whether the organism is judged to be colonizing or infecting. In addition, susceptibility to alternative antimicrobial agents will need to be considered carefully. To date, the most frequently isolated glycopeptide-resistant bacteria, often recovered in pure culture from significant infections, have been various species of enterococci (Table 2). As with normally susceptible enterococci, recovery of glycopeptide-resistant enterococci does not necessarily indicate a requirement for antimicrobial chemotherapy; drainage of pus or removal of invasive devices alone may effect cure. In the collection of strains having high-level glycopeptide resistance recovered from renal unit patients (115), all of 15 strains of *E. faecalis* were normally susceptible to penicillins. One of these agents, usually ampicillin or amoxicillin, proved appropriate for the management of uncomplicated urinary tract infection due to such strains provided that the patients were not allergic to penicillin. Most of these strains were resistant to a wide range of alternative antimicrobial agents, but susceptible to ciprofloxacin (Table 3). Ciprofloxacin, therefore, could be used for the treatment of urinary tract infection when a penicillin was inappropriate. For serious infections such as bacteremia, caused by strains of glycopeptide-resistant *E. faecalis*, the synergistic combination of a penicillin and an aminoglycoside could be used. However, the use of aminoglycosides was precluded for most of the renal unit patients by the identification of high-level gentamicin resistance (MIC, >1,000 mg/liter) in 13 of the 15 strains and high-level streptomycin resistance (MIC, >1,000 mg/liter) in all 15 (38). Transferable high-level resistance to streptomycin and kanamycin in *E. faecalis* was first reported in 1970 (73, 110) and rapidly became widespread (16, 95, 107, 127). Transferable high-level gentamicin resistance in *E. faecalis* was first reported in France in 1979 (53) and subsequently in many parts of the world (75, 88, 107, 115, 127). Some of the latter strains remained normally susceptible to streptomycin, which may occasionally be the appropriate aminoglycoside to combine with a penicillin. For the therapy of serious infections caused by strains highly resistant to both streptomycin and gentamicin and to glycopeptides, a combination of ampicillin and ciprofloxacin may

have to be considered, depending on the results of in vitro susceptibility testing. This combination is said not to be synergistic (98), but has been reported to have contributed to cure in two patients with endocarditis caused by vancomycin-susceptible strains of *E. faecalis* (107).

All 27 glycopeptide-resistant strains of *E. faecium* described by Uttley and colleagues (115) were resistant to ampicillin and also to a range of alternative antimicrobial agents, but not to high levels of gentamicin (Table 3). Of the 27 strains, however, 21 were susceptible to ciprofloxacin. Use of this agent contributed to cure of urinary tract infections due to these strains in some patients, although ciprofloxacin resistance emerged during treatment of one patient (115). Despite relatively high MICs of penicillins, there is no well-documented alternative to the use of a synergistic combination of a penicillin plus gentamicin for the treatment of serious infections due to most strains of *E. faecium* (62). Synergy should always be confirmed by in vitro testing.

This therapeutic strategy has been compromised by the isolation of at least three distinct clinical strains of *E. faecium* having transferable, high-level gentamicin resistance (24). Previously, such resistance determinants had been shown to be transferable to *E. faecium* from *E. faecalis* in vitro (17). To date, no strains of *E. faecium* with high-level resistance to both aminoglycosides and glycopeptides have been reported.

The synergistic combination of vancomycin (or teicoplanin) plus gentamicin would normally be considered a therapeutic alternative for serious enterococcal infections in patients allergic to penicillins or for strains resistant to penicillins. However, strains of enterococci with high-level glycopeptide resistance and normal susceptibility to gentamicin do not respond to the synergistic combination of vancomycin and gentamicin (C. H. Collins and A. H. C. Uttley, unpublished observation). The therapeutic dilemma posed by infections caused by high-level glycopeptide-resistant enterococci in patients in whom penicillins are contraindicated has no satisfactory solution. Alternative antimicrobial agents may be ciprofloxacin or other newer quinolones. A strain of *E. gallinarum* with low-level resistance to vancomycin (MIC, 16 mg/liter) was susceptible in vitro to its combination with gentamicin (58). However, Sahm and colleagues showed that strains of *E. faecalis* with low-level vancomycin resistance may not be susceptible to such synergy (97). Reported clinical experience in the treatment of infections due to high- and low-level glycopeptide-resistant enterococci is extremely limited. Much wider experience is required before definitive guidelines can be established.

In the therapy of infections due to coagulase-negative staphylococci showing resistance to either teicoplanin or vancomycin, it may be wise to avoid therapy with the alternative glycopeptide as such strains may develop cross-resistance. It is of interest that a strain of *S. haemolyticus* that developed low-level resistance to vancomycin during a prolonged course of vancomycin therapy was resistant to teicoplanin (MIC, 16 mg/liter) at the start of treatment (101). The infection with which this strain was associated responded eventually to treatment with a combination of vancomycin and tobramycin. This raises the possibility that the combination of vancomycin and an aminoglycoside may show synergy against coagulase-negative staphylococci with low-level resistance to glycopeptides. In view of the reports of resistance in vitro to teicoplanin among coagulase-negative staphylococci, the susceptibility of such strains should be monitored closely.

Vancomycin-resistant leuconostocs, lactobacilli, and pediococci are isolated occasionally as opportunistic pathogens in compromised patients (Table 1). Antimicrobial therapy of infections caused by these organisms is, however, relatively uncomplicated as they are usually susceptible to a number of commonly used drugs including penicillins, erythromycin, clindamycin, and gentamicin (22). Strains of *Erysipelothrix rhusiopathiae*, which may show inherent resistance to vancomycin, are susceptible to penicillins and cephalosporins (40).

The therapeutic problems encountered in infections due to glycopeptide-resistant enterococci and staphylococci, both of which may also be resistant to penicillins and aminoglycosides, have stimulated a continuing search for new antimicrobial agents. One such agent which shows promise is the lipopeptide daptomycin. Daptomycin has excellent in vitro activity against enterococci showing both high- and low-level resistance to vancomycin, gentamicin, or ampicillin (97, 99, 115). Time-kill studies have shown that daptomycin is bactericidal at four times the MIC and, in animal models of enterococcal endocarditis and pyelonephritis, it has contributed to cure (25, 72). However, clinical studies are still required to evaluate its potential for therapy of human infections. Both vancomycin-susceptible and -resistant enterococci are capable of a single-step mutation to daptomycin resistance (63, 65, 115). Daptomycin is also active against leuconostocs, lactobacilli, and pediococci (22) and both vancomycin-resistant (101) and -susceptible (25) staphylococci. Vancomycin-resistant enterococci are also susceptible to MDL 62198 (ramoplanin), a lipopeptolide; MICs of this agent are similar to those of daptomycin (115).

The management of patients harboring vancomycin-resistant bacteria entails effective treatment of individual patients and prevention of cross-infection. In the case of infection with vancomycin-resistant enterococci, the evidence available argues strongly in favor of such organisms being capable of spread in the hospital environment. Although the routes of transmission are unclear, it would seem reasonable to nurse infected or colonized patients in isolation to prevent dissemination of the organisms or the resistance determinants or both.

ACKNOWLEDGMENTS

We thank F. Sargon for help in the preparation of this manuscript. We also thank Francesco Parenti for providing the structures of vancomycin and teicoplanin.

ADDENDUM IN PROOF

A recent report has documented nine cases of bacteremia caused by vancomycin-resistant pediococci (T. D. Mastro, J. S. Spika, P. Lozano, J. Appel, and R. R. Facklam, J. Infect. Dis. **161**:956–960, 1990).

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